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Long-Term Pharmacokinetics of Transdermal Testosterone Gel in Hypogonadal Men*

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ABSTRACT

Transdermal delivery of testosterone (T) represents an effective alternative to injectable androgens. Transdermal T patches normalize serum T levels and reverse the symptoms of androgen deficiency in hypogonadal men. However, the acceptance of the closed system T patches has been limited by skin irritation and/or lack of adherence. T gels have been proposed as delivery modes that minimize these problems. In this study we examined the pharmacokinetic profiles after 1, 30, 90, and 180 days of daily application of 2 doses of T gel (50 and 100 mg T in 5 and 10 g gel, delivering 5 and 10 mg T/day, respectively) and a permeation-enhanced T patch (2 patches delivering 5 mg T/day) in 227 hypogonadal men. This new 1% hydroalcoholic T gel formulation when applied to the upper arms, shoulders, and abdomen dried within a few minutes, and about 9–14% of the T applied was bioavailable. After 90 days of T gel treatment, the dose was titrated up (50 mg to 75 mg) or down (100 mg to 75 mg) if the preapplication serum T levels were outside the normal adult male range. Serum T rose rapidly into the normal adult male range on day 1 with the first T gel or patch application. Our previous study showed that steady state T levels were achieved 48–72 h after first application of the gel. The pharmacokinetic parameters for serum total and free T were very similar on days 30, 90, and 180 in all treatment groups. After repeated daily application of the T formulations for 180 days, the average serum T level over the 24-h sampling period (C_{avg}) was highest in the 100 mg T gel group (1.4- and 1.9-fold higher than the C_{avg} in the 50 mg T gel and T patch groups, respectively). Mean serum steady state T levels remained stable over the 180 days of T gel application. Upward dose adjustment from T gel 50 to 75 mg/day did not significantly increase the C_{avg}, whereas downward dose adjustment from 100 to 75 mg/day reduced serum T levels to the normal range for most patients. Serum free T levels paralleled those of serum total T, and the percent free T was not changed with transdermal T preparations. The serum dihydrotestosterone C_{avg} rose 1.3-fold above baseline after T patch application, but was more significantly increased by 3.6- and 4.6-fold with T gel 50 and 100 mg/day, respectively, resulting in a small, but significant, increase in the serum dihydrotestosterone/T ratios in the two T gel groups. Serum estradiol rose, and serum LH and FSH levels were suppressed proportionately with serum T in all study groups; serum sex hormone-binding globulin showed small decreases that were significant only in the 100 mg T gel group. We conclude that transdermal T gel application can efficiently and rapidly increase serum T and free T levels in hypogonadal men to within the normal range. Transdermal T gel provided flexibility in dosing with little skin irritation and a low discontinuation rate. (*J Clin Endocrinol Metab* **85:** 4500–4510, 2000)

THE SKIN IS an attractive route for systemic delivery of steroids. Transdermal preparations of testosterone (T) provide a useful delivery system for normalizing serum T levels in hypogonadal men and preventing the clinical symptoms and long-term effects of androgen deficiency (1–5). Currently available transdermal patches are applied to the scrotal skin (Testosderm) or to other parts of the body (Androderm and Testoderm TTS). The former requires preparation of the scrotal skin with hair clipping or shaving to optimize adherence of the patches. The permeation-enhanced T patch (Androderm) is associated with skin irritation in about a third of the patients, and 10–15% of subjects have been reported to discontinue the treatment because of

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chronic skin irritation (6, 7). Preapplication of corticosteroid cream at the site of application of the Androderm patch has been reported to decrease the incidence and severity of the skin irritation (8). The most recently approved nonscrotal T patch (Testoderm TTS) causes less skin irritation (itching in about 12% and erythema in 3% of the subjects), but adherence of the patch to the skin poses a problem in some subjects (9, 10). Despite these limitations of local irritation and adherence to skin, the various T patches provide a steady state delivery of T to the circulation that mimics the normal diurnal rhythm of serum T at the low to mid normal adult male range (11–17). The long-term use of these transdermal androgen delivery patches has been shown to be efficacious in maintaining sexual function, secondary sexual characteristics, and bone and muscle mass in hypogonadal young and elderly men (5, 18–21).

T and other steroids can also be applied to the skin in open systems. When T is applied to the skin surface as a hydroalcoholic gel, the gel dries rapidly, and the steroid is absorbed into the stratum corneum, which serves as a reservoir. The reservoir in the skin releases T into the circulation slowly over several hours, resulting in steady state serum levels of the hormones (22). Our previous short-term (7–14 days) pharmacokinetic studies of both T and 5α-dihydrotestosterone (DHT) transdermal hydroalcoholic gels showed that the androgens were absorbed, and peak levels of the applied androgens occurred 18–24 h after initial application. With continued application of the gel for 7–14 days, steady serum levels of androgens were maintained (23, 24). About 9–14% of the T in the gel applied to the skin is bioavailable (24). We also demonstrated that application of the T gel (100 mg/day) at a single site or four separate sites resulted in serum T levels at the upper limit of the normal range, with about 23% higher serum levels when the gel was applied at four sites. In the 7- to 14-day studies, neither T nor DHT gel produced skin irritation in the small number of subjects studied (23, 24). In the present study we investigated the detailed pharmacokinetics and tolerability of T gel (AndroGel) at two dosages (50 and 100 mg/day) and T patch after repeated daily dosing for 180 days in a large number of hypogonadal men (n = 227) recruited from 16 centers across the United States.

Subjects and Methods

Subjects

Two hundred and twenty-seven hypogonadal men were recruited, randomized, and studied in 16 centers in the United States. About one third of the subjects were randomized into each treatment group (Table 1). The patients were between 19–68 yr of age and had single morning serum T levels at screening of 10.4 nmol/L (300 ng/dL) or less. The screening serum T concentrations were measured at each center's clinical laboratory. Previously treated hypogonadal men were withdrawn from T ester injection for at least 6 weeks and from oral or transdermal androgens for 4 weeks before the screening visit. Aside from the hypogonadism, the subjects were in good health, as evidenced by medical history, physical examination, complete blood count, urinalysis, and serum biochemistry. If the subjects were taking lipid- lowering agents or tranquilizers, the doses were stabilized for at least 3 months before enrollment. The subjects had no history of chronic medical illness or alcohol or drug abuse. The subjects had a normal rectal examination, a prostate-specific antigen level of less than 4 ng/mL, and a urine flow rate of more than 12 mL/s before enrollment to the study. They were excluded if they had a generalized skin disease that might affect T absorption or a prior history of skin irritability with the nonscrotal T patch (Androderm). Subjects with body weight of less than 80 or more than 140% of ideal body weight and subjects taking medications known to alter the cytochrome P-450 enzyme systems were also excluded from this study.

T gel and patch

T gel (AndroGel) was manufactured by Besins Iscovesco (Paris, France) and supplied by Unimed Pharmaceuticals, Inc. (Deerfield, IL). The formulation is a hydroalcoholic gel containing 1% T (10 mg/g). We have previously shown that about 9–14% of the steroid in the gel applied is available to the body. Thus, 10 g gel applied to the skin contain 100 mg T and delivers approximately 10 mg T to the body (23, 24). Approximately 250 g gel were packaged in multidose glass bottles that delivered 2.27 g gel for each actuation of the pump. Patients assigned to the 50 mg T in 5 g gel group were given one bottle of T gel and one bottle of placebo gel (vehicle only); those assigned to the 100 mg T in 10 g gel were dispensed two bottles of the active T gel. All patients applied T gel or placebo gel at four separate sites each day (right and left upper arms/shoulders and right and left abdomen). On day 1 of the study, the patients were instructed to depress the pump of one of the bottles once, and the gel was applied to the right upper arm/shoulder. Then, using the same bottle, a second dose of gel was delivered and applied to the left upper arm/shoulder. The second bottle was then used with the actuation of the pump for gel to be applied to the right abdomen and the second actuation to the left abdomen. On the following day, the application sites were reversed. Alternate application sites continued throughout the study. After application of the gel to the skin, the gel

TABLE 1. Baseline characteristics of the hypogonadal men

Treatment group	T patch (5 mg/day)	T gel (50 mg/day)	T gel (100 mg/day)
No. of subjects enrolled	76	73	78
Age (yr)	51.1	51.3	51.0
Range (yr)	28–67	23–67	19–68
Ht (cm)	179.3 ± 0.9	175.8 ± 0.8	178.6 ± 0.8
Wt (kg)	92.7 ± 1.6	90.5 ± 1.8	91.6 ± 1.5
Serum T (nmol/L) at screening[a]	6.40 ± 0.41	6.44 ± 0.39	6.49 ± 0.37
Causes of hypogonadism			
Primary hypogonadism	34	26	34
Secondary hypogonadism	15	17	12
Aging	6	13	6
Normogonadotropic hypogonadism	21	17	26
Yr diagnosed	5.8 ± 1.1	4.4 ± 0.9	5.7 ± 1.24
No. previously treated with T (%)	50 (65.8)	38 (52.1)	46 (59.0)
Duration of treatment (yr)	5.8 ± 1.0	5.4 ± 0.8	4.6 ± 0.7

[a] Screening serum T concentrations were measured before enrollment in each study center's clinical laboratory and not at the central laboratory.

dried within a few minutes. The patients washed their hands with soap and water thoroughly after gel application. After 90 days the subjects titrated to the 75 mg/day T gel dose were supplied with three bottles, one containing placebo and two containing T gel. The subjects were instructed to apply one actuation from the placebo bottle and three actuations from the T gel bottle to four different sites of the body as described above.

T patches (Androderm) were provided, each delivering 2.5 mg/day T, which is the recommended replacement dose for androgen replacement therapy. The patients were instructed to apply two T patches to a clean dry area of skin on the back, abdomen, upper arms, or thighs once per day. Application sites were rotated, with an approximately 7-day interval between applications to the same site. T gel or patches were applied at approximately 0800 h each morning for 180 days.

In the T gel group, treatment compliance was estimated as the percentage of T gel actually used compared with the theoretical amount of T gel that could have been used. The actual amount of T gel used was measured as the difference in weight of the dispensed and returned T gel bottles. The theoretical weight of T gel that could have been used was calculated as 2.27 g/actuation × days in study × 2, 3, or 4 actuations depending on whether the dose of T gel was 50, 75, or 100 mg, respectively. In the T patch group, the actual number of patches used was compared with the theoretical number that could have been used calculated as days in study × 2 patches/day.

Study design

The study is a randomized, multicenter (16 centers), parallel study including 2 doses of T gel and a single dose of T patches. A placebo group was not included because 6-month placebo treatment of hypogonadal men was not believed to be justifiable, as untreated hypogonadism will result in impaired libido, decreased strength, bone mineral loss, and other clinical defects. The study was double blinded until day 90 with respect to the T gel groups and open label for the T patch group. For the first 3 months of the study (days 1–90), the subjects were randomized to receive 50 mg/day T gel (in 5 g gel delivering about 5 mg T/day), 100 mg/day T gel (in 10 g gel delivering about 10 mg T/day), or 2 patches delivering 5 mg T/day (T patch). In the following 3 months (days 91–180), the subjects were administered 1 of the following treatments: 50 mg/day T gel, 100 mg/day T gel, 75 mg/day T gel, or 5.0 mg/day T patch. Patients who were applying T gel had a single, preapplication serum T measurement made on day 60; if the levels were within the normal range (10.4–34.7 nmol/L; 300–1000 ng/dL), they remained on their original dose. Men with T levels at 60 days of treatment less than 10.4 nmol/L and who were applying 50 mg T gel and those with T levels more than 34.7 nmol/L who had received 100 mg T gel were then assigned to the 75 mg/day T gel group for days 91–180. No changes in dose were made to subjects randomized to T patch.

On days 0, 1, 30, 90, and 180 subjects had multiple blood samples for T and free T measurements at 30, 15, and 0 min before and 2, 4, 8, 12, 16, and 24 h after T gel or patch application. Brief history and physical examinations were performed, and any complaints or adverse events were documented in the subject's records. In addition, subjects returned to each study center on days 60, 120, and 150 for a single blood sampling before application of the gel or patch. Serum DHT, estradiol (E_2), FSH, LH, and sex hormone-binding globulin (SHBG) were measured in samples collected before gel or patch application on days 0, 30, 60, 90, 120, 150, and 180. Sera for hormones were stored frozen at −20 C until assay. All samples for a patient for each hormone were measured in the same assay whenever possible. In addition, the subjects were examined for any adverse effects and skin irritation.

Hormone assays

Except for the screening serum T concentration, which was measured at each center's clinical laboratory, all hormone assays were performed at the Endocrine Research Laboratory of the Harbor-University of California-Los Angeles Medical Center. Serum T levels were measured after extraction with ethyl acetate and hexane by a specific RIA using reagents from ICN Biomedicals, Inc. (Costa Mesa, CA). The cross-reactivities of the antiserum used in the T RIA were 2.0% for DHT, 2.3% for androstenedione, 0.8% for 3β-androstanediol, 0.6% for etiocholanolone, and less than 0.01% for all other steroids tested. The lower limit of quantitation of serum T measured by this assay was 0.87 nmol/L (25 ng/dL). The mean accuracy (recovery) of the T assay, determined by spiking steroid free serum with varying amounts of T (0.9–52 nmol/L), was 104% (range, 92–117%). The intra- and interassay coefficients of the T assay were 7.3% and 11.1% at the normal adult male range, which in our laboratory was 10.33–36.17 nmol/L (298–1043 ng/dL). Serum free T was measured by RIA of the dialysate after an overnight equilibrium dialysis, using the same RIA reagents as in the T assay. The lower limit of quantitation of serum free T using this equilibrium dialysis method was estimated to be 22 pmol/L. When steroid-free serum was spiked with increasing doses of T in the adult male range, increasing amounts of free T were recovered, with a coefficient of variation that ranged from 11–18.5%. The intra- and interassay precisions of free T were 15% and 16.8%, respectively, for adult normal male values (121–620 pmol/L, 3.48–17.9 ng/dL).

Serum DHT was measured by RIA after potassium permanganate treatment of the sample followed by extraction. The methods and reagents of the DHT assay were provided by Diagnostic Systems Laboratories, Inc. (Webster, TX). The cross-reactivities of the antiserum used in the RIA for DHT were 6.5% for 3β-androstanediol, 1.2% for 3α-androstanediol, 0.4% for 3α-androstanediol glucuronide, 0.4% for T (after potassium permanganate treatment and extraction), and less than 0.01 for other steroids tested. This low cross-reactivity against T was further confirmed by spiking steroid free serum with T (35 nmol/L, 1000 ng/dL) and taking the samples through the DHT assay. The results even on spiking with over 35 nmol/L T were less than 0.1 nmol/L DHT. The lower limit of quantitation of serum DHT in this assay was 0.43 nmol/L. All values below this value were reported as less than 0.43 nmol/L. The mean accuracy (recovery) of the DHT assay, determined by spiking steroid free serum with varying amounts of DHT from 0.43–9 nmol/L, was 101% (range, 83–114%). The intra- and interassay coefficients of variation for the DHT assay were 7.8% and 16.6%, respectively, for the adult male range, which in our laboratory was 1.06–6.66 nmol/L (30.7–193.2 ng/dL).

Serum E_2 levels were measured by a direct assay without extraction with reagents from ICN Biomedicals, Inc. The intra- and interassay coefficients of variation of E_2 were 6.5% and 7.1%, respectively, for normal adult male range (E_2, 63–169 pmol/L, 17.1–46.1 pg/mL). The lower limit of quantitation of the E_2 was 18 pmol/L. All values below this value were reported as 18 pmol/L. The cross-reactivities of the E_2 antibody were 6.9% for estrone, 0.4% for equilenin, and less than 0.01% for all other steroids tested. The accuracy of the E_2 assay was assessed by spiking steroid free serum with an increasing amount of E_2 (18–275 pmol/L). The mean recovery of E_2 compared with the amount added was 99.1% (range, 95–101%).

Serum SHBG levels were measured by assay kits obtained from Delfia (Wallac, Inc., Gaithersburg, MD). The intra- and interassay precisions were 5% and 12%, respectively, for the adult normal male range (10.8–46.6 nmol/L). Serum FSH and LH were measured by highly sensitive and specific fluoroimmunometric assays with reagents provided by Delfia (Wallac, Inc., Gaithersburg, MD). The intraassay coefficient of variations for LH and FSH fluoroimmunometric assays were 4.3% and 5.2%, respectively, and the interassay variations for LH and FSH were 11.0% and 12.0%, respectively (adult normal male range: LH, 1.0–8.1 U/L; FSH, 1.0–6.9 U/L). For both LH and FSH assays, the lower limit of quantitation was 0.2 IU/L. All samples obtained from the same subject were measured in the same assay.

Statistical analyses

Descriptive statistics for each of the hormone levels were calculated. Before analysis, each variable was examined for its distributional characteristics and, if necessary, transformed to meet the requirements of a normal distribution. There were no significant differences between the study sites on any of the parameters; therefore, the data presented were pooled for all of the centers. The pharmacokinetic parameters for each full sampling day were determined by noncompartmental methods. The pharmacokinetics of T gel were assessed using the area under the curve from 0–24 h (AUC_{0-24}) generated by the 24 h of multiple blood sampling for T on days 1, 30, 90, and 180. The AUC was computed using the linear trapezoid method. The average T concentration over the 24 h after gel application (C_{avg}) was calculated as the AUC_{0-24} divided by 24 h.

All data in the figures and tables show the treatment mean (±SEM)

by time and/or day for each of the three groups of subjects based on the treatment from days 0–90 and for each of the five groups from days 91–180. However, because the final treatment groups (five groups) for the subjects receiving T gel were no longer randomized, statistical comparisons between groups were only performed until day 90 using the original treatment assignments (50 or 100 mg T gel or patch) as the independent groups. Comparisons between groups were performed using one-way ANOVA or the Kruskal-Wallace test (accumulation ratio, fluctuation index) followed by posttest contrasts. Analysis of the effects was performed using repeated measures ANOVA. The χ^2 test was used to compare rates. Analyses of change from day 0 to day 180 within treatment groups were performed within each of the five groups based on pattern using paired t tests. Comparisons resulting in $P \leq 0.05$ were considered statistically significant. SAS version 6.12 was used for all analyses (SAS Institute, Inc., Chicago, IL).

Results

Subjects

A total of 227 patients were enrolled: 73, 78, and 76 were randomized to the 50 mg/day T gel (T gel 50), 100 mg/day T gel (T gel 100), and T patch groups, respectively (Table 1). There were no significant differences in the patients' characteristics at baseline (height, weight, and previous T treatment). Thirty-five to 45% of the patients in each treatment group had primary hypogonadism (Klinefelter's syndrome, anorchia, testicular failure); 15–25% had well defined secondary hypogonadism (Kallman's syndrome, hypothalamic pituitary disease, pituitary tumor). The other patients had low serum T and normal or low normal LH levels. These were ascribed to aging (based on age >60 yr), or normogonadotropic hypogonadism. These patients did not have brain imaging to exclude hypothalamic-pituitary disease. Their primary physician did not deem that brain scans were indicated. After completion of day 90, 55 of the subjects in the T patch, 67 in the T gel 50, and 73 in the T gel 100 groups agreed to continue for another 3 months (days 91–180). The discontinuation rate (21 of 76, 27.6%) in the T patch group was higher ($P = 0.0002$) than those in the T gel groups (50 mg: 6 of 73, 8.2%; 100 mg: 5 of 78, 6.4%). Most of the discontinuation in the T patch group was due to adverse skin reaction based on the subjects' complaints and records. After 90 days of treatment, patients randomized initially to the T gel groups had dose adjustment if their preapplication serum T level was below 10.4 or above 34.7 nmol/L on day 60. Twenty subjects who had received 50 mg/day T gel had their dose increased to 75 mg/day; 20 who had received 100 mg/day T gel decreased their dose to 75 mg/day. The exceptions were 1 100 mg T gel patient who was adjusted to 50 mg/day and 1 50 mg T gel patient who decreased the dose to 25 mg/day. Before approval of the long-term follow-up study, 3 patients who were receiving T patch until day 90 were switched to T gel 50 from days 91–180 because of skin irritation from the patches. The data for these 3 patients as well as for the single subject who was changed from 100 to 50 mg/day were analyzed as the T gel 50 group from days 91–180. The number of subjects enrolled in the study from days 91–180 was 195, with 51 receiving T gel 50, 40 receiving T gel 75, 52 receiving T gel 100, and 52 continuing on the patch.

Treatment compliance

From days 1–90, the mean treatment compliance rates were 89.8%, 93.1%, and 96.0% for the T patch, T gel 50, and T gel 100 groups, respectively. During days 1–180 (the 6-month study period), the mean compliance rate was 86.3% for the T patch and 93.3%, 111.4%, and 96.5% for the 50, 75, and 100 mg/day T gel groups, respectively.

Pharmacokinetics of serum T concentrations (Table 2 and Fig. 1)

At baseline (day 0) average serum T concentrations over 24 h (C_{avg}) were similar in the three groups and were below the normal adult range (Fig. 1). In all three groups, during the 24-h baseline period the mean maximum T levels (C_{max}) occurred between 0800–1000 h (0–2 h in Fig. 1), and the minimum (C_{min}) T levels occurred 8–12 h later, demonstrating the expected diurnal variation of serum T.

About 35% of the patients in each group (24 of 73 subjects for the T gel 50, 26 of 78 subjects for the T gel 100, and 25 of 76 subjects for T patch) had C_{avg} within the lower normal adult male range on day 0. (The C_{avg} of serum T levels at baseline in the subjects with normal serum T on day 0 were 13.3 ± 0.4, 13.3 ± 0.5, and 13.0 ± 0.5 nmol/L in the T patch, T gel 50, and T gel 100 groups, respectively.) However, over 55% of these subjects had one or more serum T measurements below 10.4 nmol/L during the course of day 0. All except three of the subjects met the enrollment criterion of serum T less than 10.4 nmol/L at screening (measured at each center's laboratory). These three subjects were enrolled during a brief period when the admission serum T level was raised to 12.1 nmol/L (350 ng/dL) or less by the sponsor. The C_{avg} of serum T in the three treatment groups on day 90 after transdermal T application was different between those with low (T patch, 11.8 ± 0.8; T gel 50, 17.2 ± 1.2; T gel 100, 25.9 ± 1.4 nmol/L) or normal (T patch, 14.5 ± 0.7; T gel 50, 25.1 ± 2.4; T gel 100, 29.5 ± 1.9 nmol/L) baseline serum T levels. This was anticipated; however, statistical analyses with two-way ANOVA showed that the status (C_{avg}) of serum T at baseline of more than or less than 10.4 nmol/L had no significant interaction with treatment. Thus, the differential response to transdermal T treatment was not confounded by the pretreatment serum T concentrations. Inclusion of these subjects did not influence the pharmacokinetic results of the treatment groups. Thus, in all subsequent pharmacokinetic analyses, all subjects in a treatment group were analyzed together regardless of whether their C_{avg} of serum T on day 0 was more than or less than 10.4 nmol/L.

On day 1 after the first application of transdermal T, serum T rose most rapidly in the T patch group, reaching a C_{max} between 8–12 h (T_{max}), plateaued for another 8 h, then declined to the baseline. Serum T rose steadily to the normal range after T gel application, with C_{max} achieved by 22 and 16 h in the T gel 50 and T gel 100 groups, respectively.

On days 30 and 90, serum T followed a similar pattern as on day 1 in the T patch group. In the T gel groups, serum T levels were at steady state, showing small and variable increases after treatment. After gel application on both days 30 and 90, the C_{avg} in the T gel 100 group was 1.4-fold higher than that in the T gel 50 group and was 1.9-fold higher than

TABLE 2. Serum T pharmacokinetic parameters after transdermal application of T gel or patch

Parameters	T patch	T gel (50 mg/day)	T gel (100 mg/day)
Day 0			
C_{avg} (nmol/L)	8.22 ± 0.55	8.22 ± 0.53	8.60 ± 0.55
C_{max} (nmol/L)	10.89 ± 0.71	11.37 ± 0.72	11.55 ± 0.76
C_{min} (nmol/L)	6.07 ± 0.42	6.07 ± 0.42	6.52 ± 0.44
Day 1			
C_{avg} (nmol/L)	16.71 ± 0.82	13.80 ± 0.63	17.82 ± 0.90
C_{max} (nmol/L)	22.36 ± 1.13	19.42 ± 1.09	25.86 ± 1.39
C_{min} (nmol/L)	8.04 ± 0.53	7.90 ± 0.50	8.67 ± 0.57
T_{max} (h)	11.8	22.1	16.0
Day 30			
C_{avg} (nmol/L)	14.62 ± 0.17	19.62 ± 1.12	27.46 ± 1.18
C_{max} (nmol/L)	19.96 ± 0.92	30.37 ± 1.99	41.60 ± 1.94
C_{min} (nmol/L)	8.15 ± 0.50	12.52 ± 6.36	17.51 ± 0.94
T_{max} (h)	11.3	7.9	7.8
Day 90			
C_{avg} (nmol/L)	14.46 ± 0.68	19.17 ± 1.06	27.46 ± 1.12
C_{max} (nmol/L)	20.70 ± 1.05	29.33 ± 1.91	41.74 ± 2.31
C_{min} (nmol/L)	7.38 ± 0.46	12.27 ± 0.63	17.37 ± 0.78
T_{max} (h)	8.1	4.0	7.9

Day 180	T patch	T gel (50 mg/day)	T gel (50 to 75 mg/day)	T gel (100 to 75 mg/day)	T gel (100 mg/day)
C_{avg} (nmol/L)	14.14 ± 0.88	19.24 ± 1.18	15.60 ± 3.68	25.79 ± 2.55	24.72 ± 1.05
C_{max} (nmol/L)	20.04 ± 1.31	28.78 ± 1.81	23.58 ± 3.72	38.48 ± 3.72	37.55 ± 2.17
C_{min} (nmol/L)	7.69 ± 0.62	12.86 ± 0.86	10.47 ± 2.47	17.51 ± 1.85	16.82 ± 0.78
T_{max} (h)	10.6	5.8	2.0	7.8	7.7

C_{avg} (nmol/L), Time-averaged concentration over 24-h dosing interval determined by $AUC_{0-24}/24$; C_{max} (nmol/L), maximum concentration during 24-h dosing interval; C_{min} (nmol/L), minimum concentration during 24-h dosing interval; T_{max}, time at which C_{max} occurred.

that in the T patch group ($P = 0.0001$). The variation in serum concentration over the day [fluctuation index = $(C_{max} - C_{min})/C_{avg}$] was similar in the three groups. On days 30 and 90, the accumulation ratio, which is defined as the increase in daily exposure to T with continued transdermal application (calculated as $AUC_{day\ 30\ or\ 90}/AUC_{day\ 1}$) was 0.94 ± 0.04 for the T patch group showing no accumulation, whereas the accumulation ratios at 1.53 ± 0.09 and 1.9 ± 0.18 were significantly higher ($P = 0.0001$) in the T gel 50 and 100 groups, respectively. This indicates that the T gel preparations had a longer effective half-life than the T patch (Table 2 and Fig. 2).

On day 180, the serum T concentrations achieved and the pharmacokinetic parameters were similar to those on days 30 and 90 in those patients who continued in their initial randomized treatment groups (Fig. 1 and Table 2). For the patients who switched from T gel 50 or 100 to T gel 75, their C_{avg} on day 180 was 20.84 ± 1.76 nmol/L, midway between the C_{avg} in the T gel 50 (19.24 ± 1.18 nmol/L) and T gel 100 (24.72 ± 6.08 nmol/L) groups. Examination of Table 2 and Fig. 1 shows that the patients titrated to this T gel 75 group were not homogeneous. On day 180, the C_{avg} in the patients in the T gel 100 group who converted to 75 mg/day on day 90 was 1.7-fold higher than the C_{avg} in the patients titrated to T gel 75 from 50 mg/day. Despite adjusting the dose up by 25 mg/day in the T gel 50 to 75 group, the C_{avg} remained lower than for those remaining in the 50 mg group. In the T gel 100 to 75 group, the C_{avg} became similar to those achieved by patients remaining in the T gel 100 group without dose titration.

The increase in $AUC_{0-24\ h}$ on days 30, 90, and 180 from the pretreatment baseline (net $AUC_{0-24\ h}$) showed dose proportionality. The mean for the net $AUC_{0-24\ h}$ from day 0 to day 30 or 90 was about 1.7-fold higher for T gel 100 than for T gel 50 patients (T gel 50: day 30, 268 ± 28; day 90, 263 ± 29 nmol/L·h; T gel 100: day 30, 446 ± 30; day 90, 461 ± 27 nmol/L·h). A 4.3 nmol/L (125 ng/dL) mean increase in the serum T C_{avg} level was produced by each 25 mg/day of T gel. The increases in $AUC_{0-24\ h}$ from the pretreatment baseline achieved by the T gel 100 and T gel 50 groups were approximately 2.9- and 1.7-fold higher than those resulting from application of the T patch (day 30, 154 ± 18; day 90, 157 ± 20 nmol/L·h).

The preapplication serum T levels in the T patch group remained at the lower limit of the normal range throughout the entire treatment period. Serum T levels after T gel application reached steady state at about 1–2 days after the initial application (24). Thereafter, the mean serum T levels remained at about 17–20 nmol/L in the T gel 50 group and about 22–30 nmol/L in the T gel 100 group (Fig. 2, *upper panel*).

Pharmacokinetics of serum free T concentration

At baseline (day 0), serum free T C_{avg} was similar in all three groups (T patch, 167 ± 14; T gel 50, 154 ± 14; T gel 100, 150 ± 13 pmol/L) and was at the lower limit of the adult male range (121–620 pmol/L). The detailed pharmacokinetic parameters of serum free T on days 1, 30, 90, and 180 mirrored those of serum total T as described above (data not shown). Similar to the total T results, the free T C_{avg} achieved by the T gel 100 group was 1.4- and 1.7-fold higher than those in the T gel 50 and T patch groups, respectively ($P = 0.001$).

The preapplication mean free T levels throughout the treatment period in all three groups were within the normal

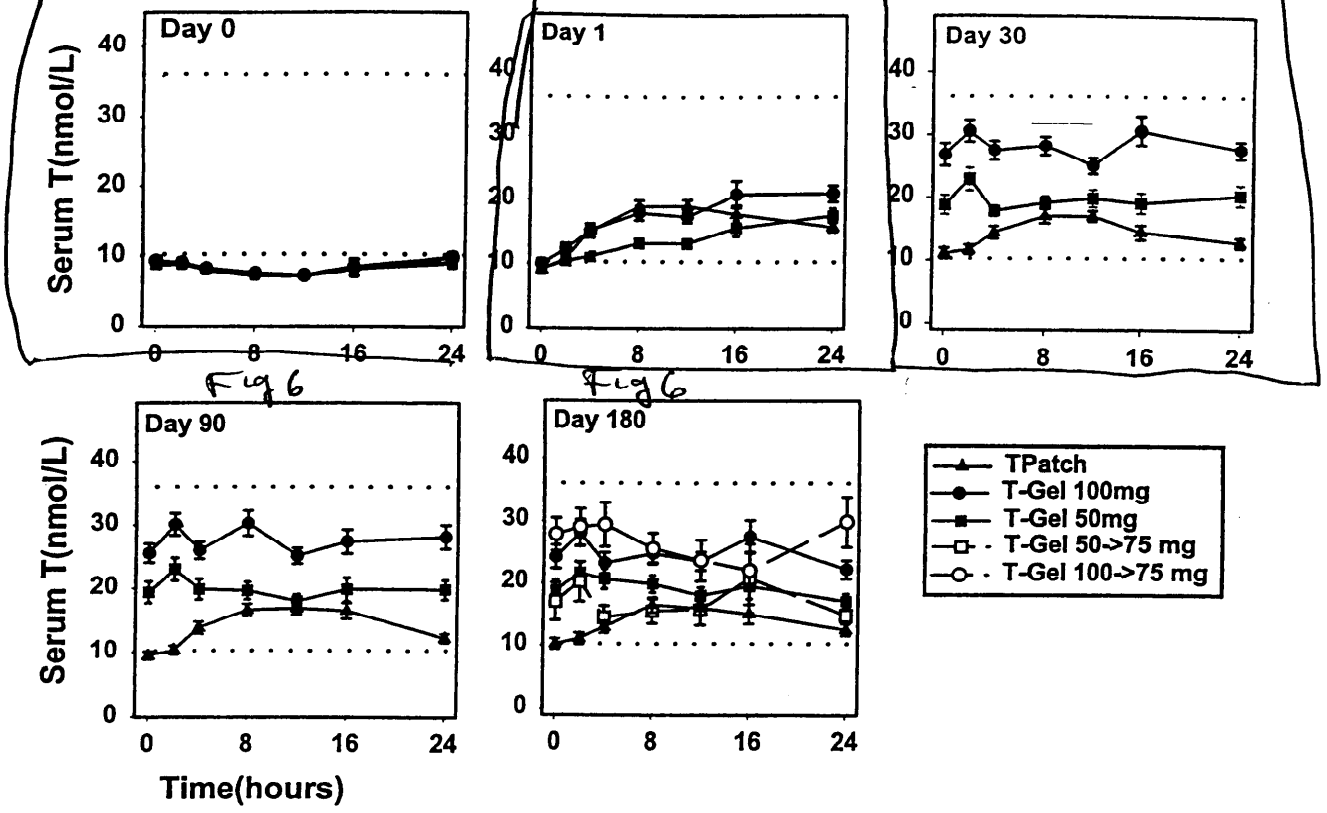

FIG. 1. Serum T concentrations (mean ± SE) before (day 0) and after transdermal T applications on days 1. 30, 90, and 180. Time 0 h was 0800 h, when blood sampling usually began. On day 90, the dose in the subjects applying T gel 50 or 100 was up- or down-titrated if their preapplication serum T levels were below or above the normal adult male range, respectively. In this and subsequent figures the *dotted lines* denote the adult male normal range, and the *dashed lines* and *open symbols* represent subjects whose T gel dose were adjusted.

range, with the T gel 100 group maintaining higher free T levels than both the T gel 50 and T patch groups (Fig. 2, *middle panel*). The calculated percent free T (free T/T × 100) remained between 1.6–2.2% before and throughout the transdermal T treatment period. Exogenous T replacement did not significantly alter the percent free T in any of the treatment groups (Fig. 2, *lower panel*).

Serum DHT concentrations

The pretreatment mean serum DHT concentrations were between 1.24–1.45 nmol/L, which were near the lower limit of the normal range (1.06–6.66 nmol/L) and were not different among the three groups (Fig. 3, *upper panel*). After T patch application mean serum DHT levels rose to about 1.3-fold above the baseline, whereas serum DHT increased to 3.6-fold (within the normal range) and 4.8-fold (at the upper limit of the normal range) above the baseline after application of T gel 50 and 100 ($P = 0.0001$), respectively, throughout the 180 days. Examination of the DHT to T ratio (Fig. 3, *middle panel*) showed that this ratio was not significantly altered in the T patch group ($P = 0.078$), whereas in the T gel 50 and 100 groups, the DHT to T ratio increased significantly from a baseline of 0.2 to between 0.23–0.29 and 0.29–0.33, respectively, during the treatment period ($P = 0.0001$ for both groups). The mean serum total androgen levels (calculated as the sum of serum T + DHT levels for each time point) achieved by T gel 100 throughout the treatment period were 1.4- and 2.5-fold higher than those in the T gel 50 (~20 nmol/L) and T patch (~10 nmol/L) groups, respectively ($P = 0.0001$; Fig. 3, *lower panel*). Adjustment of the T gel dose on day 90 did not significantly affect the serum DHT levels, DHT/T ratios, or total androgen levels.

Serum E_2 concentrations

The baseline mean serum E_2 levels were at the lower normal range and were not different in the three treatment groups. After transdermal T application, mean serum estradiol increased to stable levels by an average of 9.2% in the T patch during the treatment period, 30.9% in the T gel 50 group, and 45.5% in the T gel 100 group ($P = 0.001$; Fig. 4).

Serum SHBG concentrations

The serum SHBG levels were similar and within the adult male range in the three treatment groups at baseline. After T replacement, serum SHBG levels showed a small decrease in all three groups ($P = 0.0046$; data not shown), which was most marked in the T gel 100 group (baseline, 26.6 ± 2.0; day 90, 23.6 ± 2.7; day 180, 24.0 ± 1.7 nmol/L; $P = 0.0095$).

Suppression of serum gonadotropin levels

Because of the wide variability in the baseline serum LH and FSH levels, these were expressed as the percent change from baseline in response to T replacement (Fig. 5). The mean

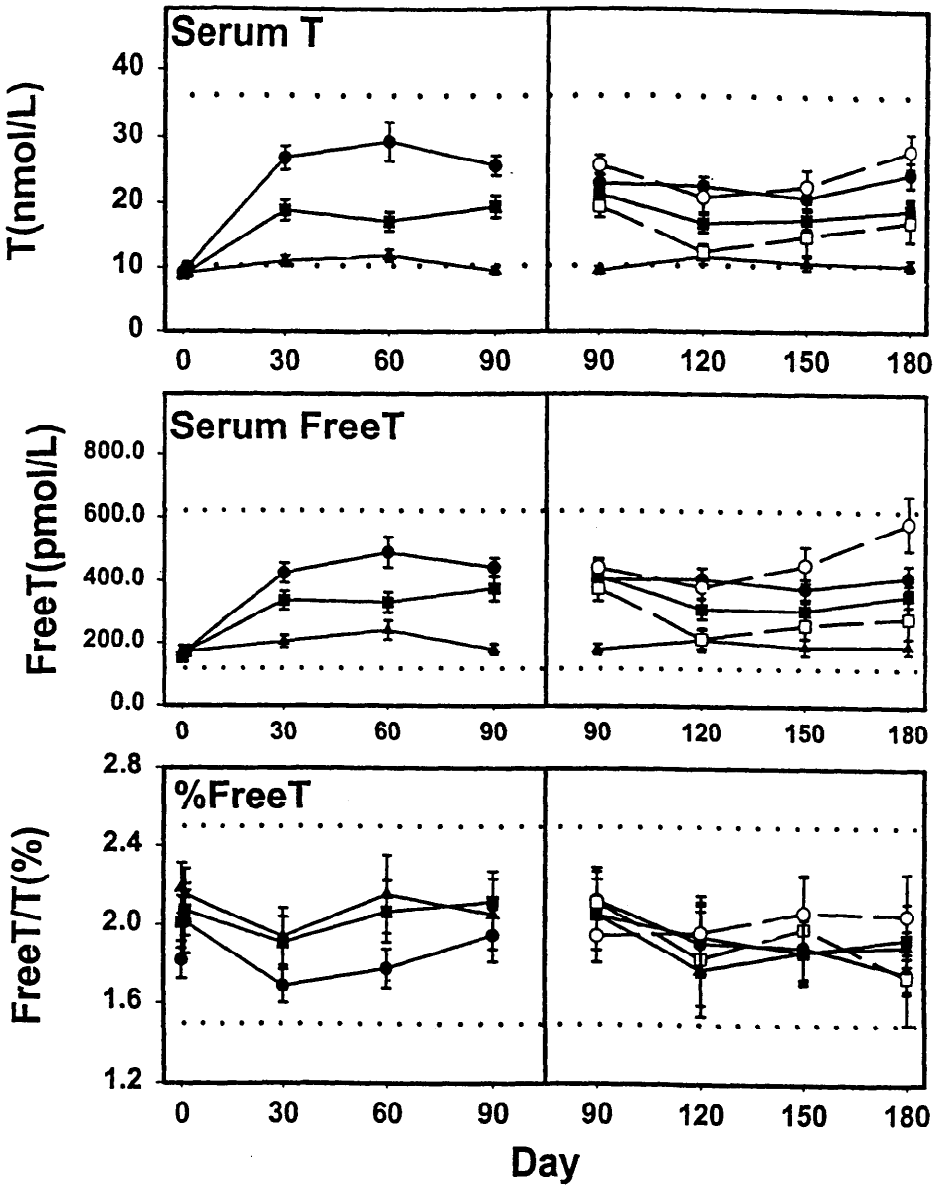

FIG. 2. Preapplication serum T (*upper panel*), free T (*middle panel*), and percent free T (*lower panel*) concentrations during daily treatment with T gel or patch from days 1–90 (*left panel*) and days 90–180 (*right panel*). On day 90, the dose in the T gel groups was changed in some subjects, as described in Fig. 1. ▲, T patch, ■, T gel 50; ●, T gel 100; □, T gel 50 to 75; ○, T gel 100 to 75.

percent suppression of serum LH levels was least in the T patch group (between ~30–40%), intermediate in the T gel 50 group (between ~55–60%), and most marked in the T gel 100 group (between ~80–85%; $P < 0.01$). The suppression of serum FSH paralleled that of serum LH levels. In the subjects with primary hypogonadism, mean serum LH and FSH levels were suppressed to within the normal range after both doses of T gel administration, but remained above the normal range after T patch application. The suppression of serum gonadotropins occurred in all hypogonadal subjects regardless of the classification of hypogonadism.

Discussion

We have shown in this study that transdermal application of this new hydroalcoholic T gel formulation (AndroGel) to a large area of skin (arms, shoulders, and abdomen) at 50 and 100 mg/day (in 5 and 10 g gel, delivering approximately 5 and 10 mg T/day, respectively) resulted in dose proportional increases in serum T in a large number of hypogonadal men. After the first application of T gel, serum T levels gradually climbed to reach a maximum level after 48–72 h, as shown in our previous report (24). On repeated application, as illustrated by the pharmacokinetics, parameters on days 30, 90, and 180 remained remarkably similar and steady serum T levels were maintained, with small and variable peaks of serum T after each application. The T levels achieved with the T patch showed little evidence of accumulation (accumulation ratio, ~1) with repeated application. The accumulation ratios were higher in both T gel groups (1.5–1.9) on day 30, consistent with the longer lasting elevations of serum T. With continued application of T gel, the accumulation rates showed no further increases, suggesting no further accumulation on days 90 and 180.

Dose titration of T gel to 75 mg was initiated after day 90 in the hypogonadal men who had serum T levels above or below the normal range. Because of study design there was

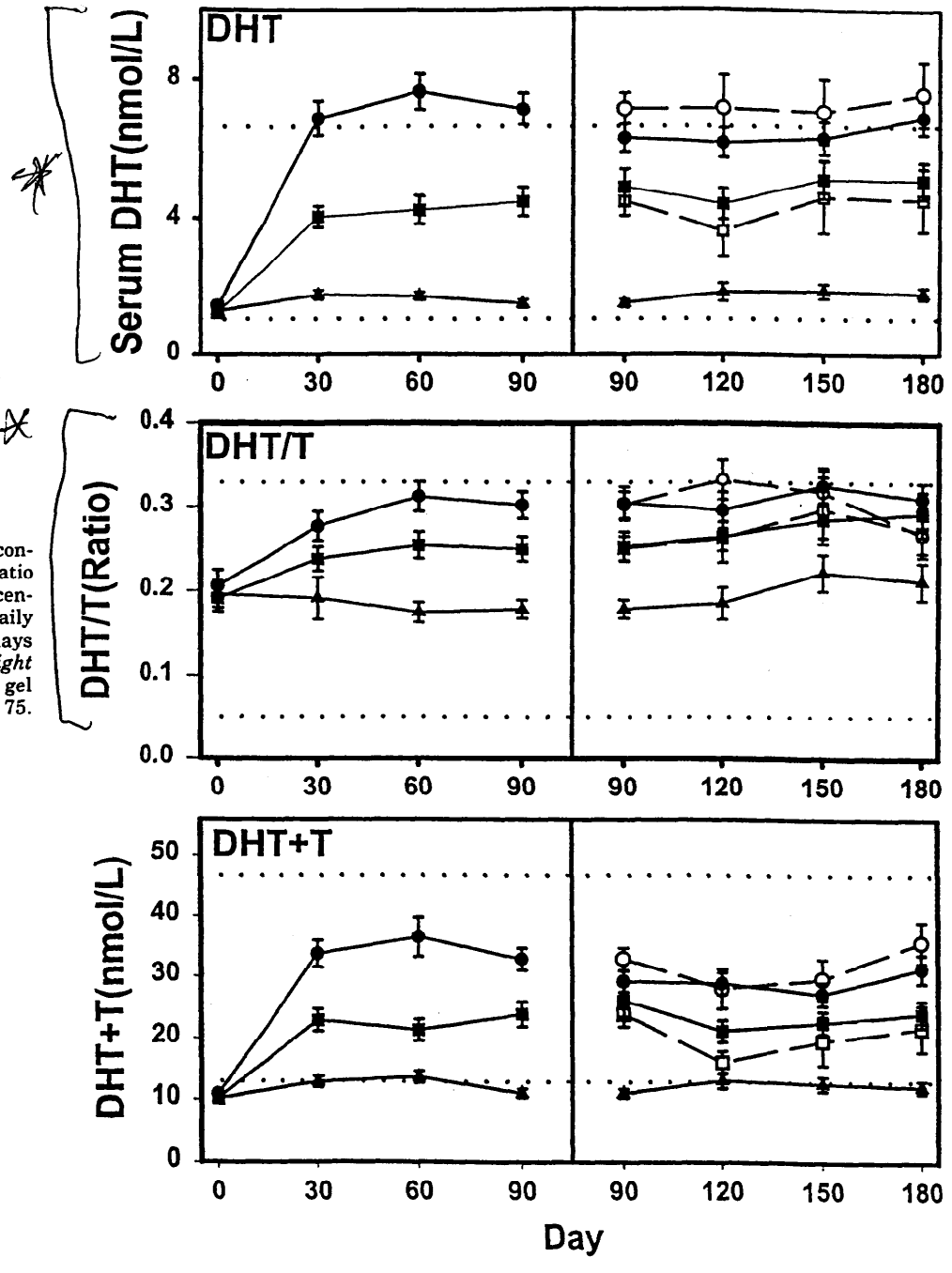

FIG. 3. Preapplication serum DHT concentration (*upper panel*), DHT/T ratio (*middle panel*), and DHT and T concentrations (*lower panel*) during daily transdermal T treatment from days 1–90 (*left panel*) and days 90–180 (*right panel*). ▲, T patch; ■, T gel 50; ●, T gel 100; □, T gel 50 to 75; ○, T gel 100 to 75.

no dose adjustment within the T patch group. Increasing the number of T patches to three or four a day could have resulted in increases in the mean serum T concentrations (16), but might have led to an even higher dropout rate because of skin irritation in some subjects. The patients who were converted from the T gel 50 to 75 mg/day, despite increasing the dose by 50%, had average serum T levels lower than those remaining in the T gel 50 group. It is uncertain whether these lower responders to T gel might be less compliant or are biologically different. The former may be possible in some individuals, as about one third of the subjects had a lower mean compliance rate of 80%, and the average serum T levels attained were related to the mean compliance rate. Alternatively, some patients might have low absorption and high clearance of T either in the basal state or after induction by exogenous T. Downward titration of the T gel dose from 100 to 75 mg/day was effective in decreasing the mean serum T level in the group by 15% and lowering the serum T concentration to the normal range in 16 of 19 of these hypogonadal men.

The present study examined a new transdermal open system, T gel, together with the available standard closed T patch system. A placebo group was not included because of ethical problems associated with withdrawing or delaying T

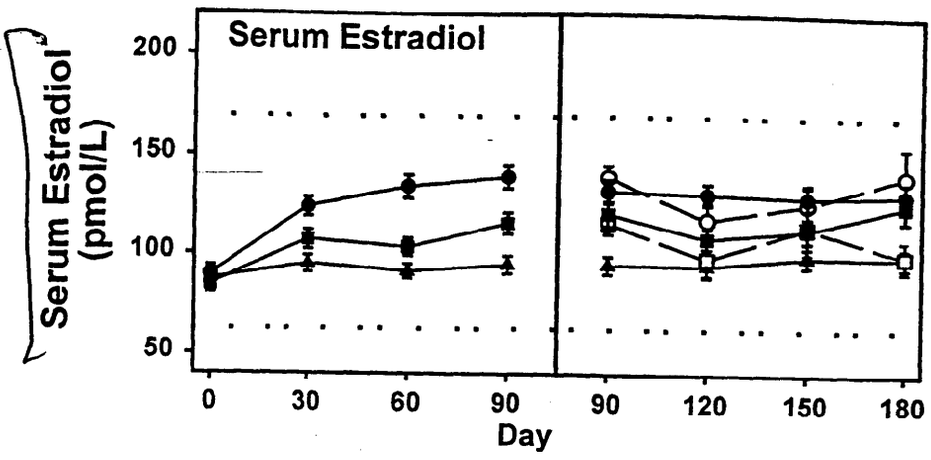

FIG. 4. Serum E_2 levels during transdermal T treatment from days 1–90 (*left panel*) and days 90–180 (*right panel*). ▲, T patch; ■, T gel 50; ●, T gel 100; □, T gel 50 to 75; ○, T gel 100 to 75.

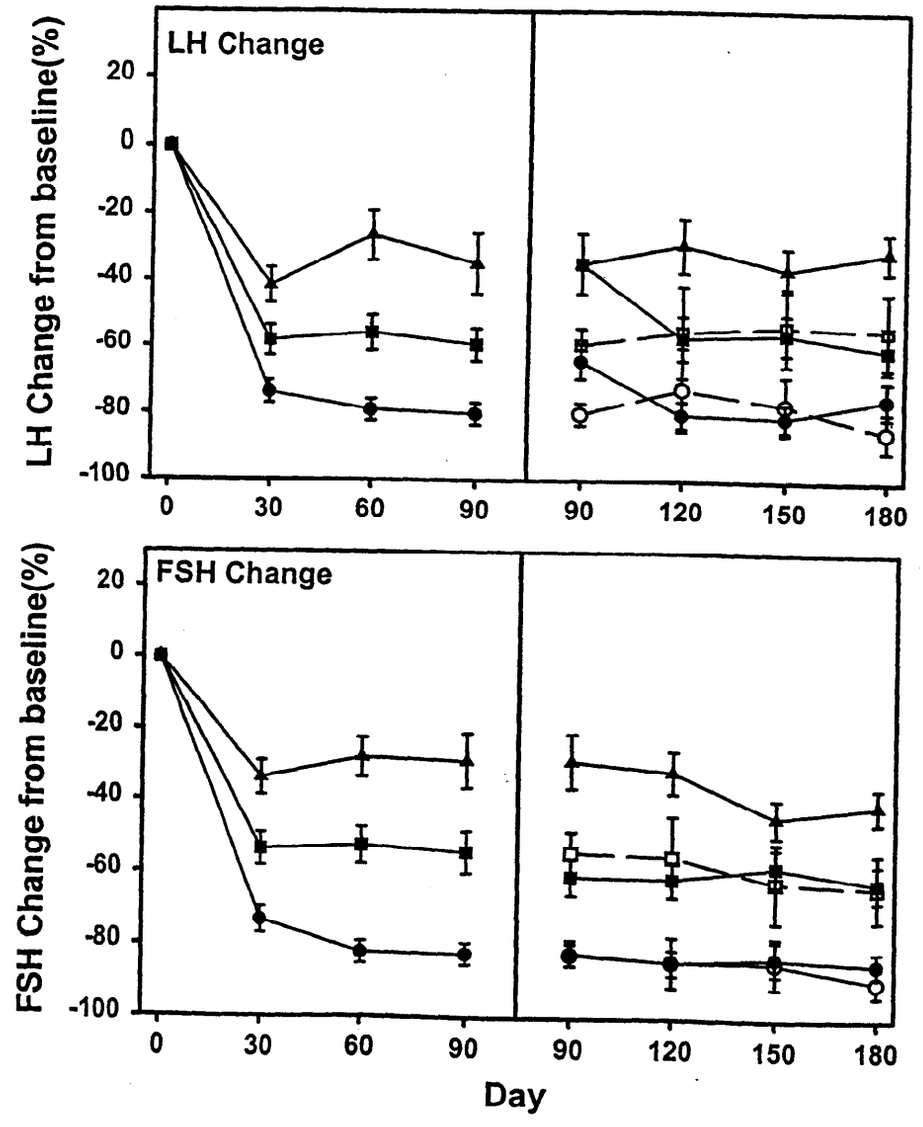

FIG. 5. Percent change in serum LH (*upper panel*) and FSH (*lower panel*) from baseline values after transdermal T replacement therapy from days 1–90 (*left panel*) and days 90–180 (*right panel*). ▲, T patch; ■, T gel 50; ●, T gel 100; □, T gel 50 to 75; ○, T gel 100 to 75.

replacement in hypogonadal men for a prolonged 6-month study period. Despite a relatively higher dropout rate, pharmacokinetic data obtained from this large group of hypogonadal men treated with this T patch were similar to those previously reported (14, 15).

Serum free T levels rose after transdermal T gel or T patch

application, paralleling those of serum T. The percent free T did not change significantly with T treatment. The results were corroborated by the small decreases, probably not clinically significant, in serum SHBG observed after transdermal T replacement in all three groups. The results indicated that when T is administered by the transdermal route, the lack of the first pass effect of the liver resulted in minor, if any, decreases in SHBG.

T gel application resulted in mean serum DHT that tripled after application of 50 mg T gel and rose nearly 5-fold with 100 mg T gel treatment. As 5α-reductase is present in nongenital skin (25), the increase in DHT/T ratios in the 100 and 50 mg gel groups could be explained by the higher conversion in the skin of T to DHT as a result of the large area of skin surface exposed to T in the gel groups compared with the very small area of skin exposed to the T patch. Increased DHT/T ratios have been observed with the transdermal scrotal patch, where even greater DHT/T ratios were noted (11–13). DHT is a potent androgen that is not back-convertible to T or aromatizable to E_2. Serum levels of T and DHT are not equivalent in all aspects of biological action, but certainly both have major actions on multiple androgen-dependent target organs. The biological impact of the moderately greater increase in DHT after T gel application is unclear other than its additive effect on total androgen action. Serum E_2 levels showed small and proportionate increases after transdermal T application that may be important for the known beneficial effects of estrogens on serum lipid levels, vascular endothelium reactivity, and bone resorption.

The biological activity of the T replacement in the hypogonadal men was evidenced by the consistent suppression of serum gonadotropin levels in the patients after transdermal T applications. The suppression of gonadotropins was proportional to the serum T levels achieved by the T patch or T gel. The marked and consistent suppression of gonadotropins observed after T gel 100 treatment suggested that such a modality of T delivery could be used in a male contraceptive regimen.

All patients were diagnosed to have male hypogonadism by their primary physician. In each of the three treatment groups, the same proportion (~30–35%) of subjects had subnormal serum T levels at screening (assayed at each center's clinical laboratory), but their average serum T levels over 24 h were within the normal range when studied at baseline (on another day and assayed at the central laboratory). Serum T in a population of men is to a great extent a continuum. The selection of men that had serum T levels below 10.4 nmol/L at screening would inevitably allow some subjects to have serum T above this arbitrarily defined threshold (approximately <2 SD below the mean for young adult men) on subsequent measurements. The admission criterion requiring a serum T concentration of 10.4 nmol/L or less is arbitrary and necessary for the design of a clinical study; however, there is no definite evidence that there is a threshold level of T at which biological response changes. The well known intrasubject variability from day to day and the differences between T assays using different reagents and methods might account for this discrepancy between screening and baseline levels. It is also not uncommon in clinical practice that on repeat serum T measurements, some hypogonadal patients would have serum T levels that fluctuate in and out of the statistical normal range. In practice, if symptomatic, many if not most of these men received androgen replacement therapy. The situation for assessment of pharmacokinetic parameters after administration of naturally occurring substances (*e.g.* T) poses different problems from those after administration of non-naturally occurring substances in the body. Ultimate serum levels attained in dynamic closed loop endocrine systems are complex and include integration of T levels (with endogenous serum T decreasing while serum T rises from exogenous administration), the characteristics of the formulation, the generic and individualized metabolic factors, and the duration of treatment. Although serum T levels attained in the groups with low or normal baseline levels were different, statistical analyses showed that the relative response to T transdermal treatment was not affected by the initial value. Thus, inclusion of these subjects did not influence the treatment comparison.

We conclude that transdermal T gel application can efficiently elevate serum T and free T levels in hypogonadal men into the mid to upper normal range within the first day of application, achieve steady state within a few days, and maintain serum T levels with once daily repeated applications. Although serum DHT/T ratios were raised after T gel applications, these ratios remained within the normal range. Serum E_2 levels were increased, and gonadotropin levels were suppressed in proportion to serum T levels. The pharmacokinetic profile and the dose proportionality observed after T gel application indicate that this transdermal delivery system may provide dose flexibility and serum T levels from the low to the high normal adult male range.

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